CONTRACT MANUFACTURING

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INTRODUCTION

Changes in Technology

Exciting changes are occurring in the pharmaceutical industry. Due to new advances in technology the industry is expanding more rapidly than ever before. For example, scientists are now using computers to manipulate molecules instead of having to go into the laboratory. Using computer simulations, they can design molecules that fit into cellular receptor sites. These "designer" molecules then produce desired therapeutic effects. Other scientists are using genetic manipulation to expand the realm of therapeutics. By inserting specific genetic material into mammalian, insect, and bacterial cells, cultures of manipulated cells produce hormones and other naturally occurring, physiologically active substances that are useful in the treatment of many disease states. Genes are also being inserted into embryos of farm animals; in adulthood, these animals are able to secrete therapeutically active substances in their milk and will become very low cost producers of substances that had either been in limited supply or had been very expensive to produce by other methods.

Changes in Core Business of Companies

To accommodate this changing technology, the core business of many companies will require capabilities that they do not presently have. In addition, many businesses have realized that being "prime" from Basic Research to Marketing and Distribution is no longer economically practical. Some companies have even decided to dedicate their facilities solely to research. Others have decided to exploit a particular niche. Companies that continue to be prime are becoming fewer and fewer.

Outsourcing Defined

Previously, the paradigm of the pharmaceutical industry required companies to be vertically integrated, i.e., the company itself performed all the operations required of its business. Now investors are demanding continued high financial performance. In an effort to reduce time-to-market, companies are more and more focusing their attention on their core competencies. As a result "outsourcing" has become a significant way of doing business. Outsourcing is the system of using a nonrelated company to produce materials or perform tasks for another on a contractual basis.

The New Paradigm of Doing Business

Outsourcing has resulted in the development of a new paradigm for doing business. This paradigm offers companies new opportunities for improving their bottom lines through the conversion of fixed costs to variable costs. They accomplish this by reducing or eliminating in-house production capabilities and replacing them with contract manufacturers. As a result, contract manufacturers that perform custom synthesis and produce intermediates, active pharmaceutical ingredients, and dosage forms are becoming increasingly important to the conduct of today's business.

Change from Vertical to Horizontal Integration

As a result, companies are becoming more horizontally rather than vertically integrated. Rather than expanding or upgrading their own facilities to accommodate new technology, companies that outsource have realized that a new product can be brought to market with greater speed than if they had performed all of the tasks internally. As an additional benefit they have positively affected their profitability through reduction of their need for investment in bricks and mortar.

The Virtual Company

The outsourcing industry has also spawned a new type of company, the "virtual" company. The concept of a virtual company is based entirely on the use of contract manufacturers, laboratories, and other providers of services to take a product from concept to market. Such a company is truly horizontally integrated. Furthermore, it has the advantage of requiring only a few managers to

coordinate the activities of various contractors as it conducts its business.

Supply Chain Management

A new breed of managers is developing within existing organizations that have decided to outsource. Their job is to effectively link the services of several contract manufacturers to forge a supply chain that performs all of the steps between R&D and Sales/Marketing. The resulting supply chain requires little or no investment of capital and achieves the same results previously obtained through vertical integration.

CONTRACT MANUFACTURING DEFINED

Origin

Contract manufacturing first began when one company asked another to produce for them a product that they chose not to produce themselves. Contract manufacturers can be found throughout all industries. Instead of producing their own "brand name" products, They provide production and other services to all comers. And, because their facilities are designed to be flexible, the same facility can make products for many customers.

Types

Contract manufacturers can be classified into two types, i.e., those who "supply" and those who "toll". Regardless of type, all contract manufacturers have the common denominator of providing one or more services for a fee.

Suppliers and Tollers

A contract manufacturer is one who supplies manufacturers materials for inventory. This supplier sells products from its inventory to one or more companies for their use or disposition. This type of contractor is sometimes known as an "original equipment manufacturer." On the other hand, a "toll manufacturer," or "toller," is a manufacturer who contracts to

- receive a raw material from another company.
- convert that material into another form, and
- return the converted material to the contracting company for its use or further disposition.

The basic difference between these two types of contractors is that one manufactures for its own inventory, while the other manufactures according to a custom order. To cloud this picture, either type of contractor may provide both functions.

Types of Tollers

Sellers of Excess Capacity

Companies that engage in toll manufacturing can be further classified into three fundamental types. First are companies that have more capacity than they need to produce an established product line. Rather than let that excess capacity stand idle, the companies use it for toll manufacturing to reduce the burden of salaries and overhead attached to the excess capacity while concurrently producing additional income. Pricing for services from these manufacturers are usually quite favorable, since their product line is absorbing their fixed costs. Only variable costs associated with the excess capacity are incurred.

Providers of Niche Services

The second type of toller is comprised of companies that, rather than marketing an established product line of their own, have concentrated on a niche service. Their facilities, equipment, and personnel have been designed only to accommodate specialized operations such as lyophilization and production of parenterals. Their success is dependent upon being able to lease their facilities and technology for the production of products for one or more customers. Their focus is on making products without having to worry about heavy R&D and marketing. A positive advantage for the use of this type of company is that they are less likely to compete with their customers.

Academic Institutions

The last type is comprised of academic institutions that provide assistance with custom synthesis, dosage form development, pilot-scale production, and production of clinical supplies in order to obtain additional income to support their academic programs. They have no interest in, nor are they equipped for, commercial production. Companies seeking outsourcing should be aware that students and faculty could form part or all of the staff of their operations; this may be a disadvantage when considering using this type of contract manufacturer.

HOW TO DETERMINE WHEN A CONTRACT MANUFACTURER IS NEEDED

The need for the services of a contract manufacturer can occur at any time during the developmental phases and/or

commercial manufacture of a product's life cycle. Such situations occur when

- Specialized manufacturing capabilities are required that are not available in-house.
- Assistance is needed with product and/or process development.
- The need to establish the market potential of a new product is required before investing in specialized capabilities.
- Difficulty is encountered in breaking into the manufacturing schedule in a timely manner to produce small research, clinical, or commercial batches.
- Production requirements cannot be accommodated when sales exceed capacity.
- Capacity is needed for the production of new, growing products, yet a place for the manufacture of products that are at the end of their life cycle still needs to be provided.

Advantages of Working with a Contractor

Developing companies especially can gain many advantages from working with a contract manufacturer. First, they gain access to production facilities without having to invest any of their own limited capital. Second, they instantly add a breadth and depth of expertise in pharmaceutical manufacturing to their operations that would have taken years to develop. Third, they gain the use of the contractor's operating personnel. Depending on the special niche of the contractor, the contractor's personnel will be experienced in one or more pharmaceutical specialties. These include custom synthesis; production of intermediates and active pharmaceutical ingredients; formulation development; lyophilization cycle development; aseptic processing; sterilization process development; regulatory assistance; sourcing of excipients; analytical methods development; validation of processes and methods; package development; and storage and testing of stability samples.

Disadvantages of Working with a Contractor

But, a company seeking to outsource must also be familiar with negative aspects associated with working with a contract manufacturer. A major disadvantage to developing companies is that the client is entrusting to another entity its valuable intellectual property that before was a closely guarded secret. Clients also must consider that they are but one of the contractor's many clients. As a result, due to competition for the contractor's resources, projects may not move forward as fast as a client may desire. Finally, clients incur the costs of at least a portion of the salaries and overhead of the contract manufacturer.

HOW TO SELECT A CONTRACT MANUFACTURER

Involvement of Purchasing Department

After evaluating the pros and cons of using a contract manufacturer, how is one selected? The selection process is very important to avoid disappointment later. Some companies require that all searches be conducted under the auspices of their purchasing department. In such cases, the purchasing department should be requested to initiate a search. Regardless, whether such a policy exists or not, close collaboration with the purchasing department is advisable during all of the following steps in the selection process.

List of Requirements

Begin any search by developing a list of requirements that a potential contractor must satisfy in order to be considered. Provide this list of requirements to the purchasing department. The most fortunate situation that can occur in the selection process is finding that the Purchasing Department is already employing a contract manufacturer with the capabilities to perform the required task.

Referrals from Colleagues

After developing the list of requirements, begin your search by seeking referrals from colleagues in the industry. There is nothing better than obtaining a recommendation about a particular contract manufacturer from someone that has successfully used its services. You can question your colleagues about any idiosyncrasies they experienced with the operations of recommended contractors. These queries can also explore the degree of satisfaction experienced regarding the manufacturer's compliance with mutually agreed upon requirements. Finally, an opinion can be obtained regarding the qualifications of the contractor's personnel assigned to projects. Be sure to solicit information as to how those personnel interrelate with customers.

Use of Information Sources

Contract manufacturers can be identified by their specialty through the use of commercial information sources (1, 2) and by review of advertisements in trade journals (3).

Commercial information sources solicit profiles of contract manufacturers for their databases. Contract manufacturers usually advertise their services in journals having the widest circulation within an industry. Many of these journals print annual buyer's, guides in which their advertisers are grouped according to the services they provide. The Internet is also a useful tool to identify contract manufacturers. Several sites are listed in the Reference section (4).

Trade Shows

Trade shows provide excellent opportunities to seek out and meet contract manufacturers. Contract manufacturers operate exhibits where literature on their companies can be obtained for later evaluation. Talking with the exhibitor's personnel provides an opportunity to conduct preliminary discussions with contractors about the services they offer. You can determine on the spot whether or not a particular contractor will be suitable for your project.

Trade shows often feature speakers on topics concerned with contract manufacturing. Attend such programs to familiarize yourself with the intricacies of contract manufacturing. You will find that your notes and handouts from the speakers will contain the latest information on this subject.

The Interview Process

Once you have identified a list of potential contractors, begin communicating with them by telephone. Table 1 provides suggested questions that can be used during interviews. Begin the interview by explaining that you are conducting a search for a contractor, and that they have been preliminarily identified as having the capability to meet the requirements of your upcoming project. Then, request them to send the most current information about themselves and their capabilities. To assure due diligence in your search, include at the conclusion of each interview a request for them to give you the names of any other contractors that they feel might be able to meet your requirements. Additional contractors identified in this manner should be contacted and interviewed, especially those who were suggested by more than one other company.

"Very Good" vs. "Excellent" Contractors

A few contractors have reached the point of being identified as being "very good" at what they do. Once this status has been reached, their business usually increases and downtime decreases. However, the nature of a contractor's business poses problems with advancing further in status, i.e., involvement with many customers, frequent changeovers of equipment, and production of many batches of a multiplicity of products. Advancing to the status of being "excellent" presents a unique challenge, because an "excellent" contractor is one that manages schedules so that time is allocated for concentration upon the nuances of any one process, smoothing out the rough edges, and achieving perfection. Your search should strive to identify the "excellent" contractors.

Confidentiality Agreement

After a list of "finalists" has been assembled, execute a confidentiality agreement with them. Only after such an agreement has been executed between your company and the contractor should the project be discussed in greater detail. Once provided with detailed knowledge of the project, the potential client and contractor can then determine whether a match exists between the requirements of the project and the contractor's capabilities.

Agenda for First Meeting with Selected Contractor

The final step in the process is to select one of the finalists and to request a meeting to discuss the project in greater detail. A sample agenda for such a meeting is contained in Table 2. Any information that the contractor will require in preparation for this meeting should be provided before the meeting. Additional meetings will probably be required before work can be initiated.

Statement of Work

Following the initial meeting, the contractor will evaluate the information provided. A prudent contractor will then provide an itemized proposal describing the work that would be necessary to be completed before the client's product can be introduced into the production schedule. The contractor and client should meet as often as necessary until both sides can agree upon a statement of work to be provided by the contractor that will accomplish the goals of the client.

DEVELOPING A CONTRACT

Basic Elements and Governing Procedures

The parties involved in developing a manufacturing contract generally understand that the contract will include

Table 1 Questions to be used when defining requirements sought in a contract manufacturer

1. What services are to be provided by the contractor?
   - Formulation development?
   - Processdevelopment?
   - Experience with and the capability to produce a particular dosage form?
   - What manufacturing capacity is required?
   - Testing laboratories?
   - Document preparation and editing?
   - Capability for distribution?
   - Regulatory assistance?
   - Aseptic processing?
   - Lyophilization?
   - Terminal sterilization?
   - Validation?
   - Quality assurance?
   - Inspection?
   - Labeling?
   - Packaging?
   - Stability studies?
2. Does the contractor have the capability, facilities, and capacity to manufacture both clinical supplies and commercial products? (Otherwise, approval of another manufacturer will have to be obtained before the product can go to market.)
3. How flexible is the contractor with regard to formulation, manufacturing, quality assurance, labeling, and packaging?
4. Are "turn key" services such as development, control, and distribution available?
5. Do the manufacturing facilities conform to current good manufacturing practices ?
6. Does the contractor allow inspection of the facilities?
7. Does the contractor allow the client to audit the manufacture of each batch of a client's product?
8. Does the contractor have an established process to monitor and improve quality?
9. Does the contractor supply a list of minimum requirements that are expected of its clients?
10. Does the contractor provide a product information questionnaire to be completed before a project begins?
11. Does the contractor insist that both parties review and approve master batch records before their use?
12. Does the contractor require that a representative of the client be on site during the manufacture of the client's product, or require that the client have a knowledgable person on-call at all times to provide immediate response to questions that arise during manufacturing?
13. Does the contractor offer analytical support? Is this support adequate?
14. Does the contractor provide a protocol of analysis or a certificate of compliance for each lot of product at the time of shipment as well as copies of completed batch records?
15. What is the contractor's policy regarding loss of customer supplied materials when the loss is due to its own negligence, or its failure to perform according to mutually agreed upon standards or obligations?
16. Does the contractor encourage innovation rather than maintaining the status quo? What examples of new practices, procedures, etc., can it describe?
17. Will the contractor provide a letter of access to its facilities master file?
18. What is the contractor's relationship with regulatory authorities?
19. What is the contractor's posture during regulatory inspections?
20. Does the contractor offer aonfidentiality agreements?
21. Is the contractor willing and able to enter into long-term supply agreements?
22. Is the contractor selling the excess capacity of its parent company?
23. Can the contractor comply with the established timetable?
24. How responsive is the contractor's customer service department?

(*Continued*)

Table 1 Questions to be used when defining requirements sought in a contract manufacturer (*Continued*)

25.	Is the contractor an equal opportunity employer?
26.	Has the contractor had experience in supplying materials for government contracts?
27.	Does the contractor produce any products for its clients that are shipped or sold internationally?

The answers to the above interrogatories will help in the selection of a contractor who can provide the services desired.

a definition of what is to be manufactured, what the cost will be, and when the product is to be delivered. Beyond these basic elements, the client and contractor are well advised to jointly develop written procedures that detail how the client and contract manufacturer are to interact and thus ensure that appropriate actions are taking place. These procedures can either be included in the contract or take the form of mutually agreed upon internal operating procedures. Further, the contract must specify how the client reviews and approves all processes specific to the manufacture of the drug product. The client is then obligated to generate operating procedures that describe the mechanisms that will be used for review and control and provide these to the contractor. The client has the added responsibility of having written procedures in place to ensure that the contractor complies with all previously agreed upon requirements. A copy of these procedures must be given to the contractor, providing awareness of the client's standards.

Conformance to Precepts

Basically, the contract must ensure that the client can expect the highest level of professionalism from the contractor, that a high quality product is being provided, and that the product is being produced according to cGMP at a fair price. The contract manufacturer is only selling its services and its quality process; therefore, conformance to these precepts is the reason for being selected as your contract manufacturer. A list of the clauses usually incorporated into a standard supply agreement for Goods and Services is included in the Appendix to this article.

Table 2 A Sample agenda for an initial meeting with a contractor

I.	Welcome and introductions
II.	Tour of contractor's facilities
III.	Detailed description of project
IV.	Question and answer period with contractor's staff
V.	Client's requirements and expectations
VI.	Contractor's requirements and expectations
VII.	Agreement to proceed with or discontinue further discussions
VIII.	Development of timetable and identification of milestones, if appropriate
IX.	Business issues
X.	Adjournment

COSTS

Contractor's Fee for Service

What does it cost to use a contract manufacturer? Although contract manufacturing may seem expensive, the use of a contractor does enable a client to dedicate its resources to more productive activities than maintaining a variety of production facilities. In return for providing the client with other opportunities for its resources, the contractor expects to receive a fee commensurate with its investment in capital equipment, wages and benefits for personnel, materials to be supplied, overhead, batch size, and a reasonable profit.

Fee Based on Expected Business

However, there is no set fee that can be universally applied to a contractor's services. Remember, in most cases a contractor, unlike a regular manufacturer, has no product line. Whether or not it has business is entirely at the whim of its customers. The quantity of business available to the contractor is governed by how well a client's products are doing in the clinic or in the marketplace. The contractor can make a guess as to how much business it will do each year, but the uncertainty is great. Therefore, a contractor usually bases his fees on the costs associated with each batch to be produced, rather than the projected total output of its production each year. To gain discounts, clients must be prepared to offer reasonable guaranteed production requirements.

Fee Related to Size of Batch

The size of the batch to be produced is a very important aspect to be considered when evaluating costs. Regardless

of the batch size, certain minimum charges for setup must be recovered. Obviously, the larger the batch, the more units are available over which to spread these charges, and unit costs diminish accordingly. Conversely, for the same reason, the smaller the batch size, the greater is the unit cost.

In-House vs. Using Contractor

When evaluating the appropriateness of a contractor's fee, a client must know its costs for doing the project in-house. Then it must consider whether the expense of adding the contractor's overhead and profit to the cost of goods is more than the in-house costs. Finally, a client must justify the cost of any delays in reaching the market as being more economical than the contractor's fee.

WORKING WITH A CONTRACT MANUFACTURER

Timetable

As a first step before beginning work with a contractor, both the client and the contractor must agree on a mutually acceptable timetable for completion of the project. This timetable should include decision points where reports and/or review meetings are required. Then, a principal contact at the contractor's site and one at the client's site need to be identified so as to assure that a uniform flow of communications can occur between the companies. The person assigned to be the client's principal contact will be responsible for monitoring the contractor's compliance with the timetable. Each party to the timetable must be agreeable to making revisions in the timetable should legitimate situations require.

Contractor's Input

From a contract manufacturer's viewpoint, it often appears that the client considers the contract manufacturer only as a provider of services with no expectation of providing input into the process of bringing the drug product to market. For a successful relationship this concept must be reexamined. Actually, the mutual best interest of both is best served by each acting as a partner of the other, freely sharing information that assures mutual success.

Communications

A contract manufacturer brings more than just a manufacturing facility to the partnership. The contractor is not just another pair of hands. The contract manufacturer and its client must be able to communicate with one another as equals and with respect for each other's contributions.

Key to Successful Relationship

The client is well advised to listen to advice provided by the contractor and respect any concerns. After all, the contractor, while being careful to protect confidences, can call upon years of experience gained from working with other clients to provide insight into problems, regulatory concerns, etc., which a client may be experiencing for the first time.

Master Production Batch Information

Open channels of communication assure continued cooperation and successful outcomes. Encourage your contractor to have timely discussions with you concerning any problems or concerns experienced with the manufacturing process or with regulatory matters. Likewise, share with the contractor your data and any other information concerning analytical results, results from focus groups, any product complaints, and conclusions from clinical studies. By working together, adjustments can be made to manufacturing processes that will assure that a quality product is being produced. When using a contractor, always remember the following: A successful relationship can only occur when both parties work together to win.

Before the contractor can begin manufacturing activities, master production batch information must be developed. This master information package normally includes specifications for raw materials, components, analytical methods, finished product specifications, packaging instructions, and any other information pertinent to the product. The client is obligated to review and approve the master production information before allowing the contractor to proceed. This approval indicates that the client is satisfied that the contractor will be producing a product that will meet specifications.

Client's Representatives

A representative of the client should be present in the contractor's facilities during the production of the product. If the client elects not to have a representative present, the client should provide the contractor with the name of an authorized person who can be contacted at any time, day and night, to resolve any issues with the production which might occur during processing.

DISADVANTAGES TO WORKING WITH A CONTRACT MANUFACTURER

Use of Commercial-Sized Equipment for Small Batches

Some contract manufacturers are equipped to produce only commercial-sized batches of product. Because of this, the same equipment is also used for the production of smaller research and development scale batches. This is a disadvantage when batches are small, particularly where expensive materials in short supply are to be produced, because a considerable amount of bulk formulated product may not be able to be converted into finished product. Some materials will always be hung up in processing equipment, regardless of size. The materials that are hung up are not available for further processing. The quantity of hung up materials is related to the size of the processing equipment being used, and is relatively constant for that equipment. Unfortunately, when losses are being calculated, the smaller the batch size that is being produced in equipment designed for larger batches, the greater is the percentage loss of product.

Buy-Back Arrangements for Specialized Equipment

Another consideration when working with a contract manufacturer is whether specialized or dedicated processing equipment will be required. If dedicated or special equipment is required, the contract manufacturer may feel justified to ask the client to supply this equipment with or without a later buy-back arrangement. In a buy-back arrangement, the contractor asks the client to initially assume the full risk of loss of the capital investment in the equipment should the product not become a viable commercial entity. However, as the product successfully completes each stage of the steps to marketability, the client's capital investment would be gradually returned. The end result is that the contract manufacturer has all of the equipment needed for the manufacture of commercial-sized batches of the client's product at the time it is finally commercialized.

Liability

Then there is the question of liability. If an adverse event occurs in a client's own operation, the client absorbs the financial loss as a cost of doing business. How much liability for loss of product or materials during the manufacturing process should a client then expect a contractor to assume? A contractor will argue that, even though a separate entity, during the time the contractor is manufacturing the client's product, the contractor's facility is an extension of the client's shop floor. Therefore, should an adverse event occur during production of the client's product, the contractor will expect the client to absorb any financial losses as if the losses had occurred in the client's own operation. Whether or not a client agrees with this argument, the amount of liability to be assumed by each party must be agreed upon during contract negotiations.

REGULATORY ISSUES

Status of a Contract Manufacturer

From a regulatory standpoint, Regulatory agencies do not differentiate a contract manufacturer from any other manufacturer under their jurisdiction. A contract manufacturer must comply with the same federal, state, and local regulations as would any other manufacturer. In the United States, prior approval must be obtained from the U.S. Food and Drug Administration (FDA) before a contractor can be used as either the primary or alternative manufacturer for a registered pharmaceutical product. Even though a contractor is being used, the contracting company still retains primary responsibility for assuring that the contract manufacturer complies with all of the commitments that were included in the product's registration and with all aspects of current good manufacturing practices (cGMPs).

Inspections

Regulatory agencies inspect contract manufacturers on a regular basis to ensure that these manufacturers are in compliance with cGMPs. In the United States, all reports of inspections by regulatory agencies are available to anyone through freedom of information. Any company contemplating the use of a contract manufacturer should review the regulatory history of all companies under consideration as part of the selection process. Likewise, client companies, as part of their contractual relationship, should have a contractual requirement that the contractor notify them should there be an inspection involving their product, or should there be any adverse findings from any inspection which would affect the continued supply of their product by that manufacturer.

Pre-approval Inspections

Regulatory Agencies also conduct pre-approval inspections as part of the process of review of registration

documentation. Prior to a pre-approval inspection, the client and the contractor should review all documentation that will be reviewed during the inspection. Clients should also assure themselves that the contractor is, indeed, in compliance with cGMPs.

International Considerations

If the client is marketing the product internationally, the client should provide the contract manufacturer with copies of the regulatory requirements that might affect the client's product in all countries in which the product is being marketed. A contractor cannot be held responsible for compliance with regulations with which the contractor is unfamiliar.

Master Files

A contract manufacturer should be willing to provide its clients with authorization to permit the regulatory authorities to reference the facilities master file that the contractor maintains in the archives of the regulatory authority. Or, if a facilities master file is not an appropriate vehicle for a particular type of registration, the contractor should provide sufficient information about its processes and procedures to enable a client to satisfy the requirements for manufacturing information in its application for the registration of its product. Although it is convenient to be able to use contractor-supplied information in the preparation of an application for registration of a product, the client must always completely review that information to ensure that, from a regulatory viewpoint, control of the product has not been inadvertently transferred to the contractor.

Special Requirements of the Biotechnology Industry

The biotechnology industry is one of the biggest users of contract manufacturing. Contract manufacturers are used to produce bulk active pharmaceutical ingredients by cell culture and/or fermentation. Then, other contractors may be used to convert the bulk active pharmaceutical ingredients into finished dosage forms. The regulations governing the use of multiple companies for these production activities are continually being refined by the FDA.

Dedicated Equipment

In some situations, the regulatory agency will require that dedicated equipment be used in manufacturing activities. Should this requirement be imposed, many contractors require the client to purchase this equipment. This becomes another initial expense that must be added to the total cost of using a contract manufacturer.

Common Regulatory Theme

Regardless if the product is a "traditional" pharmaceutical or is a product of biotechnology, one common regulatory theme is always present. That is, the company employing a contractor retains responsibility for the product being manufactured and for ensuring that the contractor remains in compliance with the terms of the license and with cGMPs.

History of Contractor's Relations with Regulatory Agencies

Finally, before working with any contract manufacturer, potential clients must be assured that the contractor has a satisfactory history of cooperation with regulatory authorities. This type of information can be obtained from a review of several establishment investigation reports (available through freedom of information in the United States) involving that contractor.

Cooperation with Regulatory Agencies

Should a contractor regularly take an adversarial stance when dealing with regulatory authorities, there is more at stake than just defending that contractor's position. That contractor is potentially placing the continued production of the client's products in jeopardy especially if the dispute involves processes or procedures related to those products. For that reason alone, a potential client should not select that particular contractor for their project.

MONITORING THE CONTRACTOR

Quality Assurance Initial Audits

Prior to establishing any relationship with a contractor, the quality assurance staff of a potential client must audit the contractor's facilities. During this audit, the contractor should be willing to provide a comprehensive tour of the facilities. Following the tour, the auditors need to review all of the contractor's standard operating procedures that may apply to their company's proposed project. In addition, the auditors need to review the quality improvement process being used by the contractor and the results of that process.

Any concerns that have been identified during the audit should be discussed with the contractor at that time.

Actions to be Taken Upon Receipt of Audit Report

Upon completion of the audit, the auditors should provide the contractor with a report citing any problems which they have identified with the contractor's operation that might interfere with the contractor being able to successfully work on their company's project. The contractor should respond in writing to the audit report and address how they will handle each observation. Based on the results of their audit and the responses of the contractor, the audit team can then make a recommendation to the responsible personnel within their organization as to the acceptability of the contractor.

Representatives in Contractor's Facilities

Once manufacturing begins, most clients elect to have a representative present. The contractor should be willing to permit that representative to observe the processes in their entirety. Before any visit, however, the client must instruct its representative to comply with all of the standard operating procedures of the contractor while on the contractor's premises. Further, the extent a representative can be involved in the production process needs to be negotiated between the client and the contractor prior to sending a representative to the contractor's site.

Periodic Audits by Quality Assurance Staff of Client

After a client has established a working relationship with a contractor, the quality assurance staff of the client should be allowed to audit the contractor's facilities and operations on a regular basis, but usually not more frequently than once a year. Again, any observations concerning the contractor's operations arising from these audits require a written response from the contractor. If the responses are not satisfactory to the audit team, then the upper management of both companies must be called upon to immediately resolve the differences. Should this be necessary, the management of both parties must ensure that any proposed resolution remains within the terms of the contractual agreement.

Quarterly Meetings

Finally, it is good practice to hold quarterly meetings between the decision makers of both the client and the contractor. These meetings ensure that both companies are still aligned to achieve mutual goals. These meetings allow the contractor to participate in the client's decision-making process as performance for the previous quarter is reviewed and plans for the following quarter are presented. Topics for discussion should include the contractor's conformance to the client's expectations, regulatory issues concerning the client's product(s), the contractor's recent regulatory experiences, sales forecasts, and any other items appropriate to the occasion.

CONCLUSION

Through skillful management and control, contract manufacturers can be used to take a product from the "test tube miracle" stage through the stage of being a "production masterpiece." Virtual companies have learned to do these tasks well, and have successfully linked multiple contract manufacturers together to form the horizontally integrated company of the future.

Points to Follow When Working with a Contract Manufacturer

Working with a contract manufacturer is quite easy provided that the following points are followed:

- Finalize the decision to use a contract manufacturer early in the timetable of the project.
- Involve the contractor in decisions, e.g., formulation, components, regulatory, etc.
- Do not file specific requirements in regulatory documents without first assuring that the contractor agrees.
- The client and the contractor have mutually agreed upon the requirements of the project *before* beginning the project.
- The client has designated someone from their staff with whom the contractor can make contact *at any hour* to resolve difficulties.
- Remember the Golden Rule—Do unto the contractor, as you would have the contractor do unto you.

APPENDIX: ELEMENTS OF A CONTRACT

The following list of clauses are usually incorporated into supply agreements for goods and services. The author developed this list using his experience of over 15 years reviewing various supply agreements. Potential clients can

use this list to ensure the completeness of their agreements. Depending on the situation, additional elements may be appropriate while others may not. The aim in any contractual relationship is to achieve a win/win situation for both parties. This aim can only be accomplished through good faith and due process during the process of negotiation.

The Checklist

1. Payment terms
2. Forecasting process
3. Quality standards—Test methods
4. Pricing
5. Liabilities—Both parties
6. Specification(s) of item(s) or service(s) to be supplied
7. Transportation and limit of responsibility from the point of ownership
8. Right of audit and inspection
9. Term and renewals
10. Warranties
11. Prior approval over product or process changes
12. Confidentiality
13. Alternate supply in case of failure to supply
14. Limitations to subcontract
15. Acceptance
16. Third-party laboratory for resolution of testing disputes
17. Insurance
18. Supply over-forecast amounts
19. Firm purchase orders
20. Change of control
21. Assignment rights
22. Penalties for failure to perform
23. Stability responsibilities
24. Recall responsibilities
25. Survival
26. Exclusive/nonexclusive total requirements
27. Force majeure
28. Regulatory/state/federal law/cGMP compliance
29. Separability
30. Notices
31. Arbitration and dispute resolution
32. Governing law
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